Effects of drop-out on efficacy estimates in five Cochrane reviews of popular antipsychotics for schizophrenia

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Short title: Drop-out in Cochrane reviews of antipsychotics.

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ABSTRACT

Objective: Our aim was to find out how Cochrane reviews of five popular or frequently prescribed second-generation antipsychotics (SGAs) in the UK (olanzapine, risperidone, quetiapine, amisulpride and aripiprazole) approached the problem of high drop-out in placebo-controlled trials.

Method: We examined the following: (1) whether reviews included data from studies with a level of drop-out exceeding their stated exclusion criterion; (2) the level of missing data each efficacy outcome in each review relied upon (3) impact of excluding studies with high drop-out.

Results: All reviews included data they stated they would exclude because of unacceptable levels of attrition, four (risperidone, olanzapine, amisulpride, aripiprazole) without clear acknowledgement or justification. Several reviews also excluded data from a number of relatively low-attrition studies because of missing standard deviations.

Conclusion: Cochrane reviews of five popular antipsychotics for schizophrenia misrepresented the available evidence on their efficacy. The impact of including high-attrition studies was difficult to quantify because of the exclusion of relevant low-attrition studies. Further analysis of the efficacy of these drugs in studies with acceptable rates of attrition is required. To reduce the problem of high attrition, trialists should gather follow-up data from people who leave the double-blind process early.

Key words: Antipsychotics, randomised controlled trial, meta-analysis, schizophrenia.

(Word count 4,342)

Summations:	Currently available Cochrane reviews of five popular antipsychotics for schizophrenia included studies they stated they would exclude because of high levels of attrition, thus misrepresenting the evidence supporting their efficacy. The impact of including high-attrition studies was difficult to quantify because of the exclusion of important low-attrition studies due to missing standard deviations. Further analysis of the efficacy of these drugs in studies with acceptable rates of attrition is required. Cochrane reviews of antipsychotics are severely limited by limited reporting of data, very high attrition and lack of

	follow-up by trial researchers.
Considerations:	New low attrition studies have been published since most of these reviews were completed. This review has not looked at comparisons of second-generation antipsychotics (SGAs) with other antipsychotics or examined the adverse effects of each SGA. The SGAs included here are generally accepted to be at least equivalent to first-generation drugs - both in terms of efficacy and tolerability.

INTRODUCTION

Antipsychotic medication is currently regarded as the cornerstone of treatment for people with a diagnosis of schizophrenia. Second-generation antipsychotics (SGAs) were thought to be more effective than first-generation antipsychotics (FGAs) with less extra-pyramidal adverse effects. However, with the exception of clozapine, their superiority is increasingly under question (1). SGAs are frequently prescribed and are continually gaining in popularity in the UK (2) and across the world (3).

The clinical evidence for the efficacy of most SGAs has been the subject of several published Cochrane systematic reviews. Cochrane reviews are independent, updated regularly and highly regarded in medicine and healthcare. They have greater methodological rigour in comparison to non-Cochrane reviews (4), are much less prone to bias (5, 6) and have a considerable impact on the health policy of many countries (7). They consist of two peer-reviewed publications; a protocol and the review. The protocol specifies the topic, scope and methods used and the review reports the results of the search and efficacy analysis. The publication of protocols reduces the risk of important decisions being made after the review authors have seen the data, thus minimising the risk of author bias (for discussion, see section 2.1 of the Cochrane Handbook; 8). Deviations from the protocol are discouraged, although recognised as sometimes necessary. The current Handbook strongly encourages documentation of any changes as well as sensitivity analyses to explore their impact (8).

Our aim in this paper was to find out how current Cochrane reviews of the 5 most popular second-generation antipsychotics (SGAs) in the UK approached the problem of high drop-out in placebo-controlled SGA trials.

The importance of attrition

Attrition is a particular focus of this review because it is generally unacceptably high in antipsychotic medication trials, particularly when a placebo arm is included (9). High attrition is difficult to deal with statistically when there is evidence that

data missing for non-random reasons, as could be the case for antipsychotic trials (10). Improper management of missing data can result in non-equivalent treatment groups and biased estimates of treatment effect (11, 12).

Although a recent meta-analysis found a moderate superiority of atypical antipsychotics over placebo (13), around half of the 38 included studies were missing over half their outcome data. The authors argued it is unclear what degree of attrition will bias results (cf. 14). However medical epidemiologists and CONSORT statement authors Kenneth Schulz and David Grimes, writing in *The Lancet* in 2002, stated: "*a trial would be unlikely to successfully withstand challenges to its validity with losses of more than 20% [Sackett et al., 2000].*" (15).

If the opinions of Schulz and Grimes (15) and Sackett and colleagues (16) reflect generally accepted standards in evidence-based medicine, then serious doubts must be raised about the findings of systematic reviews of antipsychotic medication when almost all of the included trials have greater than 20% attrition (e.g., 13). Supporting this, a recent survey by the Cochrane Schizophrenia Group found psychiatrists, psychiatric researchers and carers agreed that results from trials lack credibility if they suffer from more than 25% attrition over 12 weeks (17).

Aims of the Study

The goals of this review were to find out how Cochrane reviews comparing popular SGAs to placebo dealt with the issue of attrition and whether excluding high-attrition studies would affect their results.

Material and methods

The four most frequently prescribed SGAs in the UK are, from most to least popular, olanzapine, risperidone, quetiapine and amisulpride (2). The Cochrane review of aripiprazole was also included given its rising popularity with psychiatrists and pharmacists (18).

The five relevant Cochrane reviews (19-23) were downloaded from the Cochrane website by the first author in April 2010. Only the efficacy outcomes in SGA versus placebo comparisons were examined. The following information was gathered:

Acceptable level of attrition: The level of attrition from a study outcome each review stated they would exclude (or intended to exclude).
Included studies: Whether each review only included data from studies which met their stated attrition cut-off criterion.
Acknowledgment of violation of exclusion criterion: Whether a Cochrane review which included data from studies they said they would exclude acknowledged this clearly in the text and provided a reason.
Reported findings and missing data: We calculated the proportion of missing data each efficacy outcome in each review relied upon.
Results after excluding outcomes with >50% and >25% attrition: Results after excluding data with >50% and >25% attrition were calculated using the same software (Revman 5) and statistical assumptions used by Cochrane review authors.
Management of missing data and other methodological concerns: How the review authors managed missing data and other methodological issues.

Where information was missing, every effort was made to access the original paper(s) or contact the review authors for clarification. All calculations were initially performed by PH and independently replicated by PT.

Results

Acceptable level of attrition

The level of attrition judged to be acceptable by Cochrane reviews of different SGAs varied between 40% and 50% (Table 1).

Included studies

All reviews violated their own predetermined criterion by including data from trials they said they would exclude because of the level of attrition.

Olanzapine. The olanzapine authors, who stated (p.5) they would exclude data from studies with >50% total attrition, based all their outcomes in the main olanzapine vs. placebo comparison on 3 studies with attrition between 58.6% (24, 25) and 79% (26).

Risperidone. The risperidone authors, who stated on p.8 they would exclude data from studies with >50% total attrition, based 10 outcomes either partially or completely on the results of the 6mg and placebo arms of one 8-week study (27) with combined attrition of 57%. They also included data from a study which reported an N of 24 for the risperidone and placebo arms combined, and zero attrition (28). However, according to an internal confidential report by the makers of risperidone, Janssen Pharmaceuticals, 107 people were randomised to receive risperidone or placebo in this study, 59% of whom left early. This study contributed to 2 efficacy outcomes in the review.

Quetiapine. The quetiapine authors stated on p.5 they had intended, before seeing the data, to exclude data from studies with >50% attrition. They based 7 of their 8 efficacy outcomes either entirely or partially on one or more studies with >50% total attrition, all lasting 6 weeks.

Amisulpride. The amisulpride authors, who stated (p.5) they would exclude trial outcomes with >40% attrition, based 5 out of their 8 outcomes partially on one very small 6-week study with 40.7% attrition (29).

Aripiprazole. The aripiprazole authors, who stated on p.5 they would not include trial outcomes with >40% total attrition, partially based their aripiprazole vs. placebo outcome 'poor compliance with study protocol' on data from a 4-week study with 41% attrition (30), a 4-week study with 41.8% attrition (31), a 6-week study with 46.9% attrition (32), a 4-week study with 52.2% attrition (33) and a 6-week study with 66.2% attrition (33). The outcome 'needing additional antipsychotic medication' was partially based on the results of the latter two studies. The

treatment arm attrition for one of these studies (30) was lower in the review (18%, p.53) than in the original paper (37%).

The aripiprazole authors based their 2 primary outcomes ('relapse' over short and medium terms) on one study with >50% attrition (34), however withdrawal due to deterioration was this trial's primary outcome measure.

Acknowledgment of breaking exclusion criterion

One review (quetiapine) which broke its exclusion criterion clearly acknowledged this and provided a reason. The authors stated they were surprised by the levels of attrition once they saw the data and that adherence to their original protocol (excluding studies with >50% attrition) would *"leave few data to present."* (p.5; 21). The olanzapine, risperidone, aripiprazole and amisulpride reviews included data they said they would exclude without clear acknowledgement or reason in the main text.

Reported findings and attrition

Summarising the results (see Table 1) reveals that 100% of outcomes reported in the olanzapine vs. placebo comparison are based on >50% missing data for both treatment and placebo groups, 47% (n=8) are based on >60% missing data in both groups and one is based on >70% missing data in both groups.

For the quetiapine vs. placebo comparison, 75% of reported outcomes rely on >50% missing data for both groups. Almost half of the risperidone outcomes and half of the amisulpride outcomes rely on data with >20% attrition in both groups. One outcome (needing additional antipsychotics) in the aripiprazole vs. placebo comparison relies on data with >40% attrition in both placebo and treatment groups. One outcome (poor compliance with study protocol) relies on data with attrition >30% in both groups.

Results after excluding outcomes with >50% and >25% attrition

Olanzapine. Excluding trial data where >50% and >25% of total follow-up data were missing (and excluding a study involving the treatment of clozapine discontinuation symptoms (35) eliminated all data in the main olanzapine vs. placebo comparison, resulting in an empty review. See Table 1.

Risperidone. There were a number of problems in the risperidone review. The data for 'Marder 1994b' (36) was entered the wrong way round (erroneously favouring placebo) for 2 outcomes (endpoint Brief Psychiatric Rating Scale [BPRS] total scores and Positive and Negative Syndrome Scale [PANSS] positive symptom scores), a per-protocol analysis was used for the outcome of 'needing additional antipsychotic medication' instead of intention-to-treat (ITT), data on needing concomitant sedatives was incorrectly extracted from 'Marder 1994b' (36), Global Assessment of Functioning (GAF) scores were misinterpreted as favouring risperidone when in fact they favoured placebo, standard errors (SE) were used instead of standard deviations (SD) in the analyses of average change in Clinical Global Impression - Severity (CGI-S) scores and average change in PANSS scores (total, positive and negative scale scores) and a fixed-effect analysis was used instead of random effects for the outcome of 20% change in total PANSS/BPRS scores. Finally, according to the study publication (37), study NCT00272584 defined response using PANSS scores not CGI-S ratings, therefore this study should not have contributed data to the outcome of 'no clinically significant improvement'.

Fixing these and other problems reduced the number of outcomes which were equivocal (from 10 to 9), increased the number favourable to risperidone (from 9 to 10) but had no effect on the number favourable to placebo (N=2). The previously equivocal outcomes of endpoint BPRS total scores and 'no clinically significant improvement' now favoured risperidone, while the previously drug-favourable outcome of mean change in PANSS negative symptoms became equivocal.

Excluding outcomes from the 2 trials with >50% attrition removed all data from one outcome (numbers achieving a 20% reduction in BPRS total scores), reduced the number of outcomes favouring risperidone from 10 to 9 but had no effect on the number of equivocal or placebo-favourable outcomes. Removing data with >25%

attrition reduced the number of outcomes favouring risperidone to 4, reduced the number of equivocal outcomes to 7 and increased the number of placebo-favourable outcomes to 6. Three outcomes could not be estimated due to lack of data. See Table 2 for details on outcomes and effect sizes.

Quetiapine. Three treatment favourable outcomes in the quetiapine vs. placebo comparison survived after excluding studies with >50% total attrition but these were all based entirely on the results of one study with 12 participants, lasting 3 weeks (38). Three outcomes in the original review could no longer be calculated. Removing data with >25% attrition from the quetiapine review had exactly the same effect on results as removing data with >50% attrition.

Amisulpride. No amisulpride outcomes in the original review were affected by excluding data with >50% attrition. Excluding data with >25% attrition resulted in an almost empty review. The findings were equivocal for the one remaining outcome that could be calculated (needing additional medication; 1 Randomised Controlled Trial [RCT], n=104, attrition = 18.27%, relative risk [RR] 0.97 95% confidence interval [CI] 0.51, 1.84).

Aripiprazole. One aripiprazole vs. placebo outcome (poor compliance) became equivocal after removing data from two trials with >50% attrition (33) (6 RCTs, n=1786, attrition = 30.24%, RR 0.74, CI 0.48, 1.13, no significant heterogeneity). However, because we could not establish from the review, the first author or from a related publication (39) what data from which study they used to calculate this outcome we were unsure if removing these trials was justified. The finding that people receiving aripiprazole were less likely to require extra antipsychotics remained significant (2 RCTs, n=573, attrition = 22.69%, RR 0.68, CI 0.54, 0.87, no significant heterogeneity) despite removal of data from two trials with >50% attrition (33). The remaining outcomes ('relapse' over short and medium term and needing extra benzodiazepines over a 24-hour period) were unaffected by excluding data with >50% attrition.

Two aripiprazole outcomes (poor compliance and needing additional antipsychotics) were affected by removing data with >25% attrition. As already

discussed, we were not sure whether removing studies with >25% attrition was valid for the outcome of poor compliance. Doing so resulted in the removal of data from 6 trials. Based on the remaining data from 2 trials (40, 41), participants receiving intramuscular aripiprazole were no more likely to demonstrate poor compliance with the study protocol over 24 hours (2 RCTs, n=560, attrition=3.04%, RR 0.22 CI 0.03, 1.75, no significant heterogeneity) but were still less likely to need additional antipsychotics over a 24-hour period (1 RCT, n=263, attrition=2.28%, RR 0.70 CI 0.54, 0.90) after removing data from three trials with >25% attrition (33, 42). The treatment favourable findings regarding 'relapse' at 12 and 26 weeks and needing extra benzodiazepines over a 24-hour period were unaffected by excluding >25% attrition studies.

Management of missing data and other methodological concerns

Management of missing data. For intention-to-treat analysis of binary outcomes every review stated that they assumed people leaving early had the unfavourable outcome. This assumption could favour the active treatment when drop-out is higher in the placebo arm, as is the case for the majority of outcomes reported in the reviews. In reality, the reviews had to rely upon dichotomised continuous data which incorporated 'last observation carried forward' (LOCF) assumptions. Very few papers reported binary outcomes for only those who completed the trials, meaning the review authors could not complete sensitivity analyses to explore the impact of LOCF.

Inappropriate exclusion of studies. All Cochrane reviews included a number of studies they said they had excluded, or intended to exclude, because of high levels of attrition. However the olanzapine, risperidone, amisulpride and aripiprazole reviews also excluded data from a number of other important studies with relatively low attrition because of missing standard deviations (SDs). They applied this rule to both continuous and binary data, although estimates of efficacy for the latter do not require SDs. In contrast, for continuous data Leucht and colleagues (13) inferred standard deviations from other measures of variance, such as p-values and t-values, following procedures outlined in the current Cochrane Handbook (8).

Inappropriate inclusion of studies. The risperidone review included two very low-attrition studies where all participants also received clozapine (37, 43). Both studies were negative for risperidone, in that those *not receiving it* faired significantly better on most outcomes. Their inclusion helps to explain the negative results of the Cochrane review and our own re-analysis above.

Other issues. The risperidone review failed to extract all usable data from each study. For example, data on concomitant sedative use was published in 'Potkin 2006' (44), data on average change in PANSS and CGI-S scores was published in 'Marder 1994b' (36) and data on average change in PANSS scores was also published in 'Marder 1994a' (27). None of this data was included in the relevant outcome.

INSERT TABLES 1 & 2 ABOUT HERE

DISCUSSION

Main findings

Efficacy of second-generation antipsychotics at time of each review

Quetiapine. Excluding studies with >50% attrition suggested there was little conclusive evidence, at the time the review was last updated, to determine the absolute efficacy of quetiapine in treating schizophrenia. This review included studies with more than 50% attrition, but did not appear to exclude other relevant studies. In their recent review of SGAs, Leucht and colleagues found quetiapine to have a small-moderate statistically significant effect over placebo in reducing PANSS/BPRS total scores, but the clinical significance of the difference was uncertain, the majority of included studies had over 50% drop-out and no difference in numbers achieving an important response was found (13). Whether newer low-attrition studies will show quetiapine to be efficacious than placebo remains to be seen. Further analysis is clearly warranted.

Olanzapine. Although no data remained in the olanzapine Cochrane review after excluding high-attrition studies, this was a consequence of the review authors' decision to exclude lower-attrition studies when no SDs were reported. Although a more comprehensive estimate of olanzapine efficacy is available from Leucht and colleagues (13), this is based on several studies with >50% attrition. The efficacy of olanzapine in studies with acceptable rates of drop-out requires further assessment.

Risperidone. The risperidone review authors concluded the evidence for the efficacy of this drug is "unconvincing". Such inferences cannot be made on the basis of their review, not least because it included several studies it should have excluded and excluded data from several studies it should have included. This, together with other problems, makes their results difficult to interpret. The review by Leucht and colleagues does not repeat these problems, but does include studies with unacceptable rates of attrition (13). As with olanzapine and quetiapine, further assessment of risperidone's efficacy is clearly warranted.

Amisulpride. Amisulpride was found to reduce total BPRS scores by around 7 points, which is somewhat less than the 10 points thought to be required for minimal clinical improvement (45). According to both the Cochrane review and Leucht and colleagues, amisulpride also significantly reduced the risk of non-response (13), however no response-rate data was available for studies with <25% drop-out.

Aripiprazole. According to the Cochrane review and Leucht and colleagues (13), at 12 and 26 weeks people taking aripiprazole were less likely to show at least minimal deterioration on the PANSS or CGI or were less likely to become moderately to severely uncooperative or hostile for 2 days (as rated by the relevant PANSS subscale) than those taking placebo. However whether this means aripiprazole prevents *"impending relapse"* (34) is debatable. Like most trials, participants stopped their previous antipsychotic treatment abruptly, meaning discontinuation-induced deterioration in the placebo group cannot be ruled out (46, 47).

Unfortunately the Cochrane review also unnecessarily excluded a large amount of data because no SDs were supplied. The review by Leucht and colleagues again provides a more comprehensive assessment, but the figures they quote are again based on several studies with unacceptable rates of drop-out. The efficacy of aripiprazole in studies with acceptable completion rates remains unclear.

Drop-out in clinical trials of antipsychotics.

It is disconcerting that excluding studies with unacceptable rates of attrition often resulted in an absence of efficacy data for some of the most popular drugs in the world. It is also disconcerting that so many people leave these trials early. One possibility is that the high discontinuation rate for antipsychotics is restricted to a the artificial setting of clinical trials. However a recent analysis of the Norwegian Prescription Database found that, over a 20-month period, only 43% of almost 9000 patients who picked up an initial antipsychotic prescription returned to pick up a second (48).

High discontinuation rates can also be found in effectiveness trials of antipsychotics. In the government-funded CATIE study (Clinical Antipsychotic Trials of Intervention Effectiveness), 74% of participants discontinued their antipsychotic treatment over 18 months (49). In this study, olanzapine had the lowest proportion of people discontinuing treatment (64%) while quetiapine and risperidone had discontinuation rates of 82% and 74% respectively. According to the Cochrane reviews we examined, olanzapine had the highest discontinuation rates (approx. 52% to 91%) while risperidone had the lowest (approx. 25%). The more up-to-date review by Leucht and colleagues (13), who included data from an additional 2 trials (50, 51), found olanzapine had an overall discontinuation rate of only 36%, while only 29% and 38% discontinued early from risperidone and quetiapine treatment, respectively.

Cochrane review methodology

We found Cochrane reviews varied in their stated approach to handling attrition. This means that some drugs could be judged conservatively, while others could be

judged generously. Whether it is possible or desirable for the Cochrane Schizophrenia Group to prescribe how to deal with attrition is a matter for further debate. Reporting the specific proportion of data that is missing for each outcome could allow readers to have a greater understanding of the robustness of each finding.

The assumptions that participants dropping out early have either an unchanged or unfavourable outcome could favour the active treatment group when placebo drop-out is higher. However there is a heterogeneity of response to both antipsychotics and placebo (52) and in recovery generally (53-58). A potentially more reliable method of imputing missing summary binary data has been detailed by Higgins and colleagues (59) (see also 60, 61). The impact of assumptions about missing outcomes would be better understood if, as per the Cochrane Handbook, review authors were able to test whether their findings were robust to changing them (8; see sections 8.13 and 16). To allow this, and as recommended elsewhere (14), trialists need to also provide outcome data for only those who reach study endpoint as well as continue to follow-up participants who leave early.

For continuous outcomes, the use of 'last observation carried forward' (LOCF) and 'completer-analysis' (where only those providing endpoint data are included in the analysis) as the primary analysis should be avoided (10, 12, 14). These approaches create a serious risk of bias, particularly when drop-out is related to outcome (10) and varies substantially between groups (62, 63). Although more sophisticated ways of dealing with missing continuous data exist (for recent discussion see, e.g., 10, 12, 62, 63, 64), all require data normally unavailable to review authors (e.g., individual data or summary data for completers only). No approach is likely to produce credible results when more than half the summary outcome data is missing.

Cochrane reviews are an important, valuable and relatively unbiased resource for researchers and clinicians hoping to improve treatments for people with a schizophrenia diagnosis. We stress that every review urged readers to exert great caution when interpreting their results. However it is likely that only readers familiar with the issues raised by missing data will appreciate how vulnerable the results

actually are. The review authors were severely limited by the data provided in trial publications. Trialists, in turn, are faced with the challenge of avoiding substantial drop-out while meeting the various ethical obligations involved in conducting placebo-controlled trials. Thoughtful recommendations for improving the methodology and reporting of these trials have been proposed by Leucht and colleagues (14). As these authors argue, researchers must develop ways to continue to gather follow-up data from people who leave the double-blind process.

Limitations

We have not looked at comparisons of SGAs with other antipsychotics or examined the adverse effects of each SGA. The SGAs included here are generally accepted to be at least equivalent to first-generation drugs - both in terms of efficacy and tolerability (49, 65, 66). Although the issue of attrition is clearly relevant to these comparisons too (17) we did not investigate this here.

Excluding high-attrition studies very often left only 1 or 2 small studies in the analysis. Clearly this greatly limits statistical power to detect effects, and a meta-analysis of 1 study is not a meta-analysis. The relative absence of quality data from low-attrition studies is in itself remarkable for such popular drugs.

For every SGA review studied, reported drop-out was significantly and consistently lower in treatment groups compared with placebo. We did not repeat this analysis. However it is uncertain whether drop-out is a reliable indicator of efficacy or tolerability. For example, whether the prominent subjective effects of antipsychotics (67, 68) lead to participant or rater unblinding (14, 69-71) and decreased treatment drop-out has not been investigated.

New studies have been published since these reviews were completed. Other reviews may have approached the attrition issue differently and reached different conclusions. However our purpose was to review the findings of protocol-driven reviews currently accessible to service-users and clinicians. We focused on Cochrane reviews because they are likely to have had a major impact on healthcare policy in the UK and throughout the world over the last few years (7).

Our main finding was that the olanzapine, risperidone and aripiprazole Cochrane reviews misrepresented the available evidence on the efficacy of these drugs compared to placebo, the amisulpride and quetiapine reviews less so. Despite over 15 years of research and widespread clinical use, we conclude that further analysis of the efficacy of these highly popular drugs in studies with acceptable rates of attrition is required.

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Table 1. Overview of review standards and practice, focusing on attrition

	Olanzapine[a]	Risperidone	Quetiapine	Amisulpride	Aripiprazole [e]
Stated attrition cut-off for exclusion	>50%	>50%	Formerly >50%. Currently no criterion.	>40%	>40%
% leaving treatment early (any reason).	0-6 weeks: 52.4% (206/393) 0-6 months: 57% (80/140) 52 weeks: 91.4% (181/198)	25.5% (184/722)	53.1% (271/510)	Short term: 18.5% (45/243) Med-long-term: 44.9% (31/69)	34.5% (613/1776)
% leaving placebo early (any reason).	0-6 weeks: 53.2% (109/205) 0-6 months: 64.7% (22/34) 52 weeks: 97% (66/68)	37.5% (241/643)	61.2% (126/206)	Short term: 36.2% (47/130) Med-long-term: 68.1% (49/72)	39.2% (317/809)
% total leaving early in total (any reason).	0-6 weeks: 52.7% (315/598) 0-6 months: 58.6% (102/174) 52 weeks: 92.9% (247/266)	31.1% (425/1365)	55.5% (397/716)	Short term: 24.7% (92/373) Med-long term: 56.7% (80/141)	35.98% (930/2585)
Number of efficacy outcomes where missing data in both groups is above:					

		Olanzapine[a]	Risperidone	Quetiapine	Amisulpride	Aripiprazole [e]
	20%	100% (17/17)	52.2% (12/23)	87.5% (7/8)	50% (4/8)	80% (4/5)
	30%	100% (17/17)	17.4% (4/23)	87.5% (7/8)	0% (0/8)	40% (2/5)
	40%	100% (17/17)	0% (0/23)	87.5% (7/8)	0% (0/8)	20% (1/5)
	50%	88.2% (17/17)	0% (0/23)	75% (6/8)	0% (0/8)	0% (0/5)
	60%	47.1% (8/17)	0% (0/23)	0% (0/8)	0% (0/8)	0% (0/5)
	70%	5.9% (1/17)	0% (0/23)	0% (0/8)	0% (0/8)	0% (0/5)
Outcomes from original review:[b]	Favouring placebo	0% (0/13)	9.5% (2/21)[d]	0% (0/8)	0% (0/0)	0% (0/5)
	Null outcomes	46.15% (6/13)	42.9% (9/21)[d]	37.5% (3/8)	16.6% (1/6)	0% (0/5)
	Favouring treatment	53.85% (7/13)	47.6% (10/21)[d]	62.5% (5/8)	83.3% (5/6)	100% (5/5)
Outcomes after	Favouring placebo	0% (0/0)	10% (2/20)	0% (0/5)	0% (0/6)	0% (0/5)

		Olanzapine[a]	Risperidone	Quetiapine	Amisulpride	Aripiprazole [e]
excluding >50% attrition studies:[b]	Null outcomes	0% (0/0)	45% (9/20)	40% (2/5)[c]	16.6% (1/6)	20% (1/5)
	Favouring treatment	0% (0/0)	45% (9/20)	60% (3/5)[c]	83.3% (5/6)	80% (4/5)
Outcomes after excluding >25% attrition studies:[b]	Favouring placebo	0% (0/0)	35.3% (6/17)	0% (0/5)[c]	0% (0/1)	0% (0/5)
	Null outcomes	0% (0/0)	41.2% (7/17)	40% (2/5)[c]	100% (1/1)	20% (1/5)
	Favouring treatment	0% (0/0)	23.5% (4/17)	60% (3/5)[c]	0% (0/1)	80% (4/5)

[a] Excludes outcomes from a clozapine discontinuation study with only very short-term (3-5 days) data (35).

[b] Excluding outcomes not analysed by review authors because of skewed data.

[c] All based on one 3-week study with 12 participants (38).

[d] After fixing issues detailed in text.

[e] Attrition reported here does not include participants who were withdrawn by the researchers when they showed at least minimal deterioration, as this was the primary outcome (34).

Table 2. Efficacy outcomes for risperidone vs placebo after fixing problems and excluding outcome data with >50% and >25% attrition.

Outcomes once problems fixed	Outcomes once >50% attrition excluded	Outcomes once >25% attrition excluded
No difference found	**No difference found**	**No difference found**
20% reduction in PANSS total [b]	**20% reduction in PANSS total** [b]	**20% reduction in PANSS total** [b]
4 RCTs, n=410, RR 0.64 [0.39, 1.04][a]	3 RCTs, n=280, RR 0.66 [0.34, 1.28] [a]	1 RCT, n=68, RR 1.12 [0.87, 1.44]
Difference between endpoint PANSS negative [b]	**Difference between endpoint PANSS negative** [b]	**Difference between endpoint PANSS negative** [b]
4 RCTs, n=266, WMD -0.90 [-3.06, 1.27][a]	3 RCTs, n=139, WMD -0.43 [-3.05, 2.19] [a]	2 RCTs, n=95, WMD 0.69 [-0.67, 2.05]
Quality of life	**Quality of life**	**Quality of life**
1 RCT, n=30, MD 0.80 [-5.43, 7.03]	1 RCT, n=30, MD 0.80 [-5.43, 7.03]	1 RCT, n=30, MD 0.80 [-5.43, 7.03]
Difference between endpoint PANSS general [b]	**Difference between endpoint PANSS general** [b]	**Mean change in PANSS negative** [b]
2 RCTs, n=74, WMD -5.00 [-20.37, 10.37] [a]	2 RCTs, n=74, WMD -5.00 [-20.37, 10.37] [a]	1 RCT, n=223, MD -0.50 [-1.91, 0.91]
Needing additional sedatives	**Needing additional sedatives**	**20% and 30% PANSS total reduction combined** [b]
1 RCT, n=44, RR 0.87 [0.55, 1.36]	1 RCT, n=44, RR 0.87 [0.55, 1.36]	2 RCTs, n=294, RR 0.93 [0.61, 1.44] [a]
Difference in CGI severity endpoint	**Difference in CGI severity endpoint**	**30% reduction in PANSS total** [b]
4 RCTs, n=266, WMD -0.29 [-1.18, 0.59][a]	3 RCTs, n=139, WMD -0.08 [-1.14, 0.98] [a]	1 RCT, n=226, RR 0.75 [0.53, 1.07]
Difference between endpoint PANSS total [b]	**Difference between endpoint PANSS total** [b]	**20% reduction in BPRS / PANSS total** [b]
4 RCTs, n=266, WMD -7.55 [-22.04, 6.95] [a]	3 RCTs, n=139, WMD -3.84 [-19.05, 11.37] [a]	2 RCTs, n=291, RR 0.95 [0.63, 1.42]
Difference between endpoint PANSS positive [b]	**Difference between endpoint PANSS positive** [b]	
4 RCTS, n=266, WMD -2.23 [-7.12, 2.65] [a]	3 RCTs, n=139, WMD -0.99 [-6.05, 4.07] [a]	**Favours treatment**
Mean change in PANSS negative [b]	**Mean change in PANSS negative** [b]	**Needing additional antipsychotics**
1 RCT, n=223, MD -0.50 [-1.91, 0.91]	1 RCT, n=223, MD -0.50 [-1.91, 0.91]	1 RCT, n=226, RR 0.61 [0.48, 0.78]
		Mean change from CGI baseline
Favours treatment	**Favours treatment**	1 RCT, n=223, MD 0.70 [0.42, 0.98]
No clinically significant improvement (CGI-S),	**No clinically significant improvement (CGI-S),**	**Mean change in PANSS total** [b]
2 RCTs, n=329, RR 0.68 [0.46, 1.00] [a]	1 RCT, n=202, RR 0.80 [0.67, 0.97] [a]	1 RCT, n=223, MD -6.60 [-11.93, -1.27]
Needing additional antipsychotics	**Needing additional antipsychotics**	**Mean change in PANSS positive** [b]

1 RCT, n=226, RR 0.61 [0.48, 0.78]

Mean change from CGI baseline

1 RCT, n=223, MD 0.70 [0.42, 0.98]

20% reduction in BPRS total [b]

2 RCTs, n=154, RR 0.54 [0.41, 0.71]

Mean change in PANSS total [b]

1 RCT, n=223, MD -6.60 [-11.93, -1.27]

Mean change in PANSS positive [b]

1 RCT, n=223, MD -2.80 [-4.49, -1.11]

20% and 30% PANSS total reduction combined [b]

6 RCTs, n=838, RR 0.71 [0.55, 0.92] [a]

30% reduction in PANSS total [b]

2 RCTs, n=428, RR 0.78 [0.66, 0.92]

20% reduction in BPRS / PANSS total [b]

7 RCTs, n=859, RR 0.68 [0.53, 0.88] [a]

Difference between endpoint BPRS total [b]

2 RCTs, n=171, WMD -12.69 [-17.06, -8.32]

Favours placebo

Difference between endpoint PANSS delusions [b]

1 RCT, n= 30, MD 0.70 [0.24, 1.16]

Difference in average endpoint score GAF

1 RCT, n=30, MD -4.50 [-8.38, -0.62]

Skewed

Average depression scores [b]

Verbal working memory endpoint differences [b]

1 RCT, n=226, RR 0.61 [0.48, 0.78]

Mean change from CGI baseline

1 RCT, n=223, MD 0.70 [0.42, 0.98]

Mean change in PANSS total [b]

1 RCT, n=223, MD -6.60 [-11.93, -1.27]

Mean change in PANSS positive [b]

1 RCT, n=223, MD -2.80 [-4.49, -1.11]

20% and 30% PANSS total reduction combined [b]

5 RCTs, n=708, RR 0.75 [0.56, 0.99] [a]

30% reduction in PANSS total [b]

2 RCTs, n=428, RR 0.78 [0.66, 0.92]

20% reduction in BPRS / PANSS total [b]

5 RCTs, n=705, RR 0.75 [0.56, 1.00] [a]

Difference between endpoint BPRS total [b]

1 RCT, n=44, MD -16.10 [-24.45, -7.75]

Favours placebo

Difference between endpoint PANSS delusions [b]

1 RCT, n= 30, MD 0.70 [0.24, 1.16]

Difference in average endpoint score GAF

1 RCT, n=30, MD -4.50 [-8.38, -0.62]

Skewed

Average depression scores [b]

Verbal working memory endpoint differences [b]

No data left

20% reduction in BPRS total [b]

1 RCT, n=223, MD -2.80 [-4.49, -1.11]

Favours placebo

Difference between endpoint PANSS delusions [b]

1 RCT, n= 30, MD 0.70 [0.24, 1.16]

Difference in average endpoint score GAF

1 RCT, n=30, MD -4.50 [-8.38, -0.62]

Difference between endpoint PANSS general [b]

1 RCT, n=30, MD 2.50 [0.03, 4.97]

Difference in CGI severity endpoint

2 RCTs, n=95, WMD 0.50 [0.12, 0.88]

Difference between endpoint PANSS total [b]

2 RCTs, n=95, WMD 5.54 [1.35, 9.73]

Difference between endpoint PANSS positive [b]

2 RCTs, n=95, WMD 2.30 [0.96, 3.64]

Skewed

Average depression scores [b]

Verbal working memory endpoint differences [b]

No data left

No clinically significant improvement (CGI-S)

20% reduction in BPRS total [b]

Difference between endpoint BPRS total [b]

Needing additional sedatives

PANSS=Positive and Negative Syndrome Scale; BPRS=Brief Psychiatric Rating Scale; CGI-S=Clinical Global Impression – Severity; GAF=Global Assessment of Functioning; RCT=Randomised Controlled Trial; RR=Relative Risk; MD=Mean Difference; WMD=Weighted Mean Difference. 95% Confidence Intervals for RR, MD or WMD are in parentheses.

[a]Significant heterogeneity in results.
[b]Primary outcomes (mental state)